REMARKS

I. The Office Action

Claims 1-47 are currently pending in the application. Claims 17-25 and 41-47 are under examination, and claims 1-16 and 26-40 are withdrawn from consideration. The Office withdrew the rejection of claims 23 and 25 under 35 U.S.C. § 112, second paragraph, and the rejection of claims 17-19, 24, and 25 under 35 U.S.C. § 102(b). The Office also withdrew the rejection of claims 17-25 under 35 U.S.C. § 103(a).

Claims 17-23 were newly rejected under 35 U.S.C. § 102(a) for assertedly being anticipated by Cartier-Lacave (WO 2003/047635, published June 12, 2003) and/or under 35 U.S.C. § 102(e) as being anticipated by Cartier-Lacave (US 2005/0163760) ("Cartier-Lacave"). Claims 17-25 and 41-47 also were newly rejected under 35 U.S.C. § 103(a) for assertedly being obvious over Peled et al., *Science*, *283*, 845-48 (1999) ("the Peled reference") in view of Sawada et al., *J. Exp. Med.*, *187*(9), 1439-1449 (1998) ("the Sawada reference"). The Office rejected claim 21 under 35 U.S.C. § 112, second paragraph, for assertedly being indefinite. Reconsideration of the rejections is hereby requested.

II. Pending Claims and Claim Amendments

Claim 21 has been amended to replace "immature primitive progenitors" with "stem cells," as supported by claim 17. No new matter has been added by way of the amendment.

III. The Rejection Under 35 U.S.C. § 112, Second Paragraph, Is Moot.

The Office rejected claim 21 under Section 112, second paragraph, for assertedly lacking antecedent basis for the feature "the immature primitive progenitors." Claim 21 has been amended to recite "the stem cells," rendering the rejection moot.

IV. The Rejections Under 35 U.S.C. § 102(b) Should Be Withdrawn.

The Office rejected claims 17-23 as assertedly being anticipated under 35 U.S.C. § 102(a) or (e) over the Cartier-Lacave publications. The rejection is respectfully traversed for the reasons set forth below.

The Office asserted that the Cartier-Lacave publications disclose a hematopoietic progenitor or stem cell capable of expressing a mutated form of CXCR4. The Office also asserted that "Cartier-Lacave et al. [teaches that] the natural ligand of CXCR4 is SDF-1 (parag. 0088), thereby indicating that cells with this receptor are responsive." (Office Action, page 5.) The Office noted that the Applicants' specification encompassed mutants of CXCR4. (*Id.*) Thus, according to the Office, the publications disclose an isolated population of stem cells having a transgene encoding CXCR4.

"A claim is anticipated only if each and every element as set forth in the claim is found, either expressly or inherently described, in a single prior art reference." *Verdegaal Bros. v. Union Oil Co. of CA*, 814 F.2d 628, 631, 2 U.S.P.Q.2d 1051, 1053 (Fed. Cir. 1987). Cartier-Lacave does not disclose each and every element as set forth in independent claim 17. Cartier-Lacave, for example, does not disclose the element of claim 17 requiring that the stem cells "[exhibit] improved CXCR4 signaling capability in response to low and/or high concentrations of SDF-1."

Cartier-Lacave teaches that individuals with HIV infection are predisposed to develop opportunistic infections in the central nervous system (CNS). (See paragraph 88 of the Cartier-Lacave specification.) The publications teach that gp120 (HIV coat protein) binds to CXCR4 and evokes a release of TNF-α. Thus, to prevent HIV infection of microglia, Cartier-Lacave discloses microglia that express a mutated form of CXCR4 that is incapable of binding to HIV. (See paragraph 186 of the Cartier-Lacave specification.) As an alternative to expression of CXCR4 mutants, the Cartier-Lacave specification discloses microglia that are modified in order to express an antagonist of the CXCR4 receptor to inhibit downstream signaling from CXCR4. Finally, in paragraph 33, the Cartier-Lacave specification discloses a method of treating HIV dementia complex comprising providing a hematopoietic progenitor or stem cell capable of expressing a mutated form of CXCR4, a CXCR4 ligand, or a factor capable of inhibiting downstream signaling of CXCR4. Thus, taken together, Cartier-Lacave is concerned with inhibiting the function of CXCR4, either by expressing a mutant form of CXCR4 in microglial cells or expressing an antagonist of CXCR4, but those cells do not, and cannot, exhibit improved CXCR4 signaling capability as expressly recited in claim 17. Each of claims 18-23 ultimately depends from claim 17 and,

therefore, incorporate each and every feature of claim 17. Thus, Cartier-Lacave does not disclose each element of any of the rejected claims, and the Section 102 rejection should be withdrawn.

Cartier-Lacave is concerned solely with inhibiting the binding of gp120 to CXCR4 and does not disclose stem cells with improved CXCR4 signaling capability, as claimed. In this regard, Cartier-Lacave cited the Davis reference in the paragraph disclosing microglia cells expressing mutated CXCR4. (See paragraph 186 of the Cartier-Lacave specification citing Davis et al., *J. Exp. Med.*, 186, 1793-1798 (1997) (submitted herewith).) Davis discloses that SDF-1 blocks infection by T-tropic HIV strains and that HIV envelopes can compete with SDF-1 for binding to CXCR4. (Davis reference at page 1794, column 2, first full paragraph.) Davis concludes that there is an overlap in binding sites between SDF-1 and HIV envelope proteins (gp120) and the envelope protein may mediate a signal similar to that of SDF-1. Thus, Davis teaches competition between gp120 and SDF-1 for binding to CXCR4. Read in this light, Cartier-Lacave simply discloses mutants of CXCR4 that are incapable of binding gp120 without disclosing any desired or realized effect on SDF-1 binding. Moreover, because Davis teaches that the binding sites for SDF-1 and gp120 overlap, a person of ordinary skill in the art would conclude that the CXCR4 mutants disclosed by Cartier-Lacave inhibit binding of gp120, and likely exhibit reduced or defective binding and responsiveness to SDF-1. A person of ordinary skill in the art simply would not conclude that Cartier-Lacave discloses stem cells comprising a CXCR4 transgene and exhibiting improved CXCR4 signaling capability in response to low and/or high SDF-1, as required by the rejected claims.

The Office further stated that "Cartier-Lacave et al. [teaches that] the natural ligand of CXCR4 is SDF-1 (parag. 0088), thereby indicating that cells with this receptor are responsive." It is unclear if the Office means that the cells expressing CXCR4 mutants, as disclosed by Cartier-Lacave, are responsive to SDF-1, or that CXCR4 is generally known to be responsive to SDF-1. As noted above, however, there is no indication that the CXCR4 mutants disclosed by Cartier-Lacave are capable of responding to SDF-1, and all available evidence (e.g., the Cartier-Lacave disclosure and the Davis reference) indicates that the CXCR4 mutant would not be responsive. In contrast, the CXCR4 mutants encompassed by

Applicants' disclosure "retain essentially the same biological activity of the CXCR4 protein" and modifications "do not substantially change the biological activity of the protein mutein with respect to the protein itself." (See instant application at page 18, lines 8-14.) Moreover, claim 17 and claims dependent thereon requires the stem cells comprising a transgene encoding CXCR4 to exhibit improved CXCR4 signaling capability in response to low and/or high concentrations of SDF-1. Cartier-Lacave fails to disclose this feature and, by all indications, discloses CXCR4 mutants that are incapable of responding to SDF-1. Thus, Cartier-Lacave does not expressly or implicitly disclose each and every element of claim 17, and the Section 102 rejection should be withdrawn.

V. The Rejection Under 35 U.S.C. § 103(a) Should Be Withdrawn.

Claims 17-25 and 41-47 were rejected as assertedly being obvious under Section 103(a) over the Peled reference in view of the Sawada reference. The rejection is respectfully traversed for the reasons set forth below.

The Office asserted that the Peled reference teaches human cord blood and bone marrow stem cells that have high expression of CXCR4 and improved CXCR4 signaling capability in response to low and/or high concentration of SDF-1. (See Office Action, page 8.) The Office concluded that "it would have been obvious to substitute CXCR4 transgene overexpression in isolated human cord blood or bone marrow cells for cytokine induced CXCR4 overexpression in isolated human cord blood or bone marrow stem cells because Peled et al teach the equivalency of the methods of CXCR4 overexpression for producing stem cells with enhanced homing to bone marrow." (*Id.*, page 12.)

Applicants disagree that a CXCR4 transgene is equivalent to cytokine-induced CXCR4. Applicants demonstrated that stem cells comprising a CXCR4 transgene possess unexpected properties not possessed by cytokine-induced cells. "Rebuttal evidence may also include evidence that the claimed invention yields unexpectedly improved properties or properties not present in the prior art." M.P.E.P. § 2145 (citing *In re Dillon*, 919 F.2d 688, 692-93, 16 U.S.P.Q.2d 1897, 1901 (Fed. Cir. 1990)). The M.P.E.P. also provides that "[e]vidence of unexpected properties may be in the form of a direct or indirect comparison of the claimed invention with the closest prior art which is commensurate in scope with the

claims." Section 716.02(b)(II). The Peled reference is the closest prior art cited by the Office. The Peled reference teaches that CXCR4 levels were increased by exposure of stem cells to Stem Cell Factor (SCF) and interleukin-6 (IL-6). (See Peled reference at page 848.) The authors also demonstrated that treating CD34+ cells with SDF-1 caused internalization and down-regulation of CXCR4 surface expression. (*Id.*, page 846, third column.) Treatment with SDF-1 abolished migration of CD34+ cells in response to SDF-1, and prolonged treatment with SDF-1 significantly blocked the engraftment of transplants into NOD/SCID mice. (*Id.*)

In contrast to the stem cells disclosed in Peled, the stem cells disclosed and claimed by Applicants comprise a transgene encoding CXCR4. Example 5 of the specification describes the effect of treating CXCR4-transduced cord blood CD34+ cells with SDF-1. Unexpectedly, cell surface receptor expression in CXCR4-overexpressing cells decreased only 40%, whereas control cells exhibited up to 90% receptor internalization. (See instant specification at page 41, lines 22-26, and Fig. 5Bi.) Moreover, following desensitization of CD4+ cells with SDF-1, migration of cells transduced with CXCR4 was minimally affected compared to control cells that showed a significant decrease in SDF-1-mediated migration. (*Id.* at page 41, line 26, through page 42, line 3, and Fig. 5Bii.) Thus, cells overexpressing a CXCR4 transgene are able to resist desensitization. The cytokine-treated cells, in contrast, are unable to resist desensitization and lose the ability to migrate and engraft upon high-level exposure to SDF-1. Thus, one of ordinary skill in the art would not expect cytokine-induced CXCR4 to permit a cell to resist desensitization, i.e., to exhibit improved CXCR4 signaling and reduced CXCR4 internalization in response to high levels of SDF-1.

The Sawada reference does not disclose or suggest that human cord blood or bone marrow stem cells comprising a CXCR4 transgene would resist desensitization by SDF-1. Moreover, nothing in Sawada would have allowed one of ordinary skill in the art to predict that a CXCR4 transgene would have the same effect as the cytokine-induction of CXCR4. The purpose of the study described in Sawada was to determine if chemokine receptors render mouse primary lymphocytes, i.e., mature thymocytes, susceptible to HIV infection. (See, e.g., paragraphs bridging pages 1439-1440 and pages 1443-1444 of the

Sawada reference.) To this end, the Sawada authors generated transgenic mice expressing CXCR4. The reference does not suggest generating transgenic humans or human stem cells to explore the mechanism of HIV infection, and there is nothing in the reference directing one of ordinary skill in the art to (1) isolate stem cells from a human, and (2) introduce a CXCR4 transgene into human cells. Additionally, Sawada's disclosure of a peripheral blood sample to study HIV infection in T-cells does not disclose or suggest isolating stem cells from cord blood or bone marrow. For the foregoing reasons, the rejection of claims 17-25 and 41-47 has been rendered moot-in-part by claim amendment and overcome-in-part by the comments provided above. Accordingly, the Section 103 rejection should be withdrawn.

VI. Conclusion

The pending application is in condition for allowance. The Office is invited to contact the undersigned attorney by telephone if there are issues or questions that might be efficiently resolved in that manner.

Dated: August 16, 2010

Respectfully submitted,

By _____
Heather R. Kissling
Registration No.: 45,790
MARSHALL, GERSTEIN & BORUN LLP
233 S. Wacker Drive, Suite 6300
Sears Tower
Chicago, Illinois 60606-6357
(312) 474-6300
Attorney for Applicant